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Neurorehabilitation After Stroke

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Neurorehabilitation after stroke – from bedside to the lab and back

Running title: Neurorehabilitation after stroke

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Introduction

Even with recent advances in reperfusion therapy, a majority of stroke patients will experience life changing deficits beyond the acute phase. Stroke care therefore does not end at the ICU and neurorehabilitation is a crucial component on a long path towards recovery.

Post-stroke rehabilitation is ideally delivered in a multidisciplinary team that includes physicians, therapists, nurses and other health care specialists as well as the patient and their social network. The settings for rehabilitation vary substantially from acute stroke units or ICUs over specialized rehabilitation care centers to early supported discharge. Furthermore, there are great variations regarding the type of therapy, its duration and intensity.

The at times confusing heterogeneity of approaches in post-stroke rehabilitation can in part be explained by ongoing changes of organizational and administrational factors, f. e. the growing number or specialized inpatient and outpatient rehabilitation services, the integration of specialized rehabilitation teams earlier in the recovery and changes in reimbursement and funding policies.

However, another important reason is that our understanding of mechanisms that underlie stroke recovery is still limited and therapeutic approaches are mainly not evidence-based, simply because evidence from large clinical trials is missing.

In this regard, neurorehabilitation is a dynamically changing field that is increasingly expanding. Physicians, therapists or nurses in training therefor have a unique opportunity to be an integral part of systematic change and to engage in research with fundamental impact on clinical practices.

Here, we try to highlight new developments in neurorehabilitation after stroke. Each section starts with an important clinical question that stroke specialists will encounter and links them to recent compelling findings. For further reading, we will reference new consensus-based recommendations or underline how early career stroke specialists can make an impact.

Will I get better?

Facing impairment after stroke, one of the most pressing questions for patients usually is: Will I get better? Predicting recovery after stroke is essential but difficult.

It has been suggested that recovery of an initial deficit follows an almost linear progress with a fixed improvement range [1]. This phenomenon is often referred to as ~~the~~ *'proportional recovery'* and was observed across different patient collectives and domains (upper motor, lower motor, language, neglect). While this allows mostly accurate predictions for mild to moderately impaired patients, those with severe deficits show different recovery trajectories.

To better predict stroke recovery on an individual level researchers created a multi-modal biomarker-based algorithm that incorporates clinical assessments, neurophysiological and brain imaging measures [2]. If patients show a marked impairment within a simple bedside assessment of shoulder abduction and finger extension, the functional integrity of the corticospinal tract (CST) is assessed using TMS (transcranial magnetic brain stimulation). If TMS can elicit a motor evoked potential (MEP), meaning the tract was still intact, patients can be predicted to have a notable recovery despite their initial pronounced impairment. In those without MEPs, measures of CST integrity using diffusion tensor imaging (DTI) allowed for further classification of patients who showed limited recovery or not.

One recent implementation of the algorithm in clinical practice demonstrated to be feasible, and resulted in shorter hospitalization and modified therapy content without adversely effecting outcomes. While these results indicate the importance of CST damage, other imaging approaches f. e. fMRI, multivariate machine learning analysis and resting state connectivity seem to emphasize the impact of network damage. For an overview of predictive biomarkers that are considered ready for testing in a clinical setting, see [3].

How does the brain recover from stroke?

The careful observation of behavioral and neurophysiological changes during recovery can shed light on the basic principles by which the brain overcomes sustained damage. In healthy individuals, the two motor cortices exert mutual inhibition at rest. Prior to a voluntary movement for example of the right hand, the right motor cortex releases the inhibition over the left. The *interhemispheric competition model* assumes that after stroke, the unopposed overactive inhibition from the healthy to the damaged hemisphere might impede recovery. In accordance, electrophysiology studies found that chronic stroke patients exerted a persistent pre-movement interhemispheric inhibition (IHI) from the contra- to ipsilesional motor cortex prior to movement onset [4].

Based on this idea, numerous studies using transcranial direct current stimulation (tDCS) attempted to rebalance the equilibrium in the acute stage to enhance recovery with only limited effects. However, recently it could be demonstrated that pre-movement-IHI shows no difference between patients and controls at the acute stage and only becomes abnormal at the chronic stage, when most recovery has already occurred. This finding suggests that *interhemispheric imbalance* is not a cause but rather a *consequence* of the recovery process[5].

In conclusion, the mechanisms underlying stroke recovery are important to identify new therapeutic targets and still require further careful research. Young stroke specialists will be instrumental in maximizing clinical translation of preclinical stroke research; recommendation on how to do so can be found here [6].

How do we train in therapy?

Current standards of stroke rehabilitation rely on the assumption that with practice stroke patients can "re-learn" normal movement patterns. But how can we leverage motor learning to actually improve motor function? Gait abnormalities are frequent after stroke, mostly presenting as an asymmetry in steps (one leg taking shorter steps, the other showing ~~the~~ a classical circumduction). Intuitively, one might presume that therapy should focus on decreasing this asymmetry by training patients consciously to shorten the long steps and lengthen the short step. However, the conscious control of step length is cognitively demanding and has proven to have no lasting effect. Therefore, researchers have taken a different approach leveraging after-effects seen in adaptation learning (an error-based form of learning with *low* cognitive demands) with a split-belt treadmill. Split-belt treadmills allow the operator to perturb a patient's walking pattern by controlling the speed of each belt individually (with a faster running belt leading to a shorter step length and vice versa). The counterintuitive thing to do is to train patients on the split-belt treadmill with a belt configuration that increases walking asymmetry. This leads to after-effects that exhibit an opposite asymmetry to their training, so in the case of a person post-stroke: a more symmetrical walking pattern. Leveraging these after-effects, split-belt training can improve walking patterns for up to 3 months[7]. A better understanding on how we learn to move will enable young stroke professionals to evaluate current and future rehabilitation approaches in their potential and limitations. For current best practices in adult stroke rehabilitation care, we recommend the current guidelines of the American H~~h~~eart ~~a~~A~~S~~ssociation and American ~~s~~Stroke ~~a~~Association~~AHA guidelines~~.

The how much, when and where?

The dosage of drugs for secondary prevention after stroke is well defined, but how many hours of therapy are needed to improve recovery? In studies of stroke recovery in animals, the amount of movement repetitions that show an effect on outcome range ~~are laying~~ within the hundreds. Surprisingly, these findings have not influenced clinical practice much. An Australian study with the telling title "Inactive and Alone: Physical Activity within the First Days of Acute Stroke Unit Care" [8] summarized this situation dramatically: Patients were only active about 13% of their time and were alone in their room >60% of the time. The fact that stroke patients can perform and do tolerate much higher dosages of up to thousands of repetitions suggests that this is a problem mostly due to organizational factors.

And when should we give therapy? The largest randomized multicenter trial conducted in stroke rehabilitation to date provided us with some answers to this question. The AVERT trial found that very early mobilization (on average ~ 18h after stroke) needs to be considered with caution as it was associated with a reduction of favorable outcome 3 months after stroke[9]. However, it needs to be noted that the control group in this trial started rehabilitation also early after stroke, on average ~22h after stroke. It has been shown that most behavioral recovery occurs within the first three months after stroke and delayed training after stroke in animals suggest that effectiveness might be attenuated over time. This goes so far that, at the chronic stage, it seems not to make a difference if patients perform up to 9000 repetitions of a movement. Thus, what is missing is a deeper comprehension for the dose-response association within the critical time window of the acute to subacute stage after stroke[10].

All this offers the opportunity for early career stroke specialists to create change f. e. by implementing systematic care protocols and actively documenting and enforcing rehabilitative training.

Moving forward

Many new approaches are currently developing in stroke rehabilitation, and all present early career stroke specialists a great opportunity to get involved in this exciting field. Technological interventions include tracking devices to record and monitor motor function as well as robot-assisted therapy. Other approaches try to translate results from animal research that show positive effects of an enriched environment by developing computer games for rehabilitation or leveraging virtual reality. Targeted electrical stimulation and brain-computer interfaces have shown to be effective to overcome impairment after neuronal damage to a certain degree, but further research is needed. A

Kommentiert [A1]: Reviewer #2:
The authors have responded appropriately to my comments and the additions are appreciated. The ending is a little abrupt; a final sentence might emphasize the many opportunities for early career strokespecialists to get involved in the exciting and dynamic field of stroke rehabilitation.

new concept arises with the combination of immunotherapy and behavioral therapy that seems to have promising results in animal models of stroke. And there is more to come.

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